

Patch Testing in Atopic Dermatitis

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Background: Because atopic dermatitis (AD) patients differ from non-AD patients in immunologic responses (they lack β -defensins, are more likely to react to protein allergens, and are harder to experimentally sensitize to the nonprotein allergens), patch-test responses to commercially available patch test series may differ in AD patients.

Objective: To compare responses to conventional patch tests in AD and non-AD patients and to assess the importance of specific allergens in AD.

Methods: AD patients were strictly defined by history of childhood flexural dermatitis. Patients with active disease were routinely pretreated with systemic antistaphylococcal and antiyeast antibiotics before patch testing unless contraindicated. All final patch-test readings occurred at day 7.

Results: The overall number of positive patch-test results did not differ significantly in AD patients ($n = 146$) versus non-AD patients ($n = 1,003$). There was no significant increase in nickel sensitivity. There was a nonsignificant trend toward an increased number of positive patch-test reactions to tixocortol pivalate, Compositae mix, and propylene glycol in AD patients.

Conclusion: In AD patients treated with antibiotics and systemic azoles before patch testing, the number of positive patch-test reactions is almost identical to that of non-AD patients. Patch-test reactions to components of topical medicaments may be more frequent in AD as compared to non-AD patients.

THE OBJECTIVE of this study was to compare responses to conventional patch tests in atopic dermatitis (AD) patients and non-AD patients undergoing evaluation for allergic contact dermatitis and to assess the importance of specific allergens in AD.

This study is unique in that AD patients were strictly defined by history of childhood flexural dermatitis rather than by history of respiratory atopy or family history. Also, in this study, all final readings occurred at day 7 to minimize false-positive irritant readings. Finally, these data are from a single investigator who routinely pretreats adult AD patients who have active disease with systemic antistaphylococcal and antiyeast antibiotics before patch testing unless contraindicated. This minimizes the effect of occlusive patch tests on commensal organisms that are more likely to proliferate in AD patients due to defects in innate immune response.

Background

For several reasons, conventional patch testing of AD patients could have different results from the results of testing nonatopic patients and could be of less clinical benefit.

First, atopic patients are more difficult to experimentally sensitize to nonprotein allergens and may therefore be less likely to develop allergic contact dermatitis.¹ However, a substantial amount of literature shows that positive patch-test results do occur.²⁻⁴ Hairdressers who are atopic become sensitized to permanent-wave solution and hair dye at the same rate as nonatopic hairdressers.⁵ Topical medicaments are a demonstrated source of sensitization in children with AD.⁶

Second, determining the relevance of these patch-test results is especially difficult. The underlying AD will not clear completely with avoidance of conventional contact allergens as it will in patients with purely allergic contact dermatitis. Also, AD patients tested while they have an active rash are at risk for false-positive angry-back reactions.

Third, technical issues are more problematic in AD patients. These patients often develop inflammation from occlusion such as that produced with patch-test tapes. Occlusion with synthetic fibers such as polypropylene has been shown to increase staphylococcal proliferation in human sweat more than occlusion with absorbent cellulosic

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fibers.⁷ Staphylococcal colonization may proliferate under patch-test occlusion and cause flares, acting as either a superantigen or an allergen.⁸

AD patients must be patch-tested when the test site is not inflamed. Once T helper 2 (Th2) cell-type inflammation occurs, it perpetuates itself. Filaggrin expression is reduced in AD by interleukin (IL)-4 and IL-13, even without genetic loss of function.⁹ β -Defensins are down-regulated by IL-4 and IL-13, and resultant bacterial proliferation may further increase inflammation.¹⁰

Given these differences in AD patients, their patch-test results may be expected to differ from those of non-AD patients. It is logical to attempt to decrease inflammation before patch tests are applied. Immunosuppressives may reduce patch-test reactivity, leading to false negatives. Therefore, the use of antibiotics to reduce allergenic triggers such as staphylococcal colonization in adults and children and *Malassezia* yeast in adults¹¹ may be useful as they are antiinflammatory without being immunosuppressive.

Methods

Data from our database of 1,149 patients patch-tested at University Hospitals Case Medical Center from February 2003 to March 2010 were examined with Institutional Review Board approval. AD patients were defined as those who reported a history of childhood flexural dermatitis regardless of the presence or absence of respiratory allergic symptoms. The overall rates of positive patch-test reactions in AD patients and non-AD patients were compared.

Rates of positive patch-test reactions to antigens previously reported as more common in AD patients (including nickel¹² and Compositae mix¹³) were also compared.

All patients were tested with a 75-item standard series, and many were tested with supplemental allergens as well. This resulted in a total of 70,580 allergen tests: 9,318 tests performed on 146 atopic patients and 61,262 tests performed on 1,003 nonatopic patients. Patients removed patches at home after 48 hours and returned to the clinic for patch-test readings at day 3 or 4 and at day 7.

Patients with a history of AD who had active dermatitis at the time of consultation were treated with a 10-day course of cefadroxil 500 mg twice daily and fluconazole 100 mg twice daily unless contraindicated because of allergy or interaction with other medications.

All patients abstained from applying corticosteroids or topical immunomodulators to the test site (usually the back; the anterior thighs and upper arms were rarely used as alternate sites) for 2 weeks before patch tests were

applied. Patients were tested on a maximum of 10 mg of oral prednisone daily if required to keep the test site clear or if necessary (eg, for adrenal insufficiency).

Patch-test reactions were considered positive if greater than or equal to + on the International Contact Dermatitis Research Group (ICDRG) scale at day 7 or if the day-3 or day-4 reading was greater than or equal to "doubtful" (?) and the day-7 reading was doubtful (?) according to the ICDRG scale.

Results

The overall percentages of positive patch-test reactions to items on the standard series were not statistically different between AD and non-AD patients. Of 9,318 tests performed on 146 atopic patients, 340 had positive results whereas 8,978 had negative results (raw estimate: $340/9,318 = 0.0365$). Alternatively, of 61,262 tests performed on 1,003 nonatopic patients, 2,272 had positive results, whereas 58,990 had negative results (raw estimate: 0.0371). According to results from the Generalized Estimating Equation (GEE) model that did not adjust for allergen, there was no statistically significant difference between the proportion of positive reactions observed in atopic patients (model-based estimate, 0.0427; 95% confidence limit [CL], 0.0346, 0.0527) and the proportion of positive reactions observed in nonatopic patients (model-based estimate, 0.0436; 95% CL, 0.0403, 0.0472). In particular, the odds of a positive reaction in atopic patients was estimated to be 0.98 times that of the odds of a positive reaction in nonatopic patients (0.98; 95% CL, 0.77, 1.24; $p = .86$).

Table 1 shows a demographic comparison between the atopic and nonatopic groups. Atopic patients were significantly younger than nonatopic patients.

Table 2 shows a comparison for specific allergens. Of all the allergens tested, only chloroxylenol (PCMX) was statistically associated with atopic status.

Nickel-positive patch-test results were not significantly different between the two groups; 20.86% of the AD patients and 19.10% of the non-AD patients had positive patch-test reactions to nickel ($p = .62$).

Table 1. Demographics of Patch-Tested Patients

Feature	Atopic Dermatitis Patients	Nonatopic Dermatitis Patients	p Value
Age	40.01 $\pm$ 18.08 (N = 145)	50.59 $\pm$ 16.73 (N = 995)	< .0001
Male	34/146 (23.3%)	377/1003 (37.6%)	.0008
Caucasian	126/146 (86.3%)	904/1003 (90.1%)	.16

Table 2. Positive Patch-Test Reactions That Differed Most between Atopic and Nonatopic Groups

<i>Allergen</i>	<i>No. of Atopic Patients Tested</i>	<i>No. of Atopic Patients with Positive Test Results</i>	<i>% of Atopic Patients with Positive Test Results</i>	<i>No. of Nonatopic Patients Tested</i>	<i>No. of Nonatopic Patients with Positive Test Results</i>	<i>% of Nonatopic Patients with Positive Test Results</i>	<i>p Value</i>	<i>Test Used</i>
PCMX	136	4	2.94	911	7	0.77	0.02	Pearson
Imidazolidinylurea	136	6	4.41	916	19	2.07	0.09	Pearson
Neomycin sulfate	138	20	14.49	934	189	20.24	0.11	Pearson
Compositae mix	53	4	7.55	266	8	3.01	0.11	Pearson
Tixocortol pivalate	135	7	5.19	912	25	2.74	0.12	Pearson
Stearyl alcohol	135	3	2.22	911	7	0.77	0.13	Fisher
Sandalwood oil	46	1	2.17	281	0	0	0.14	Fisher
Propylene glycol	135	9	6.67	912	36	3.95	0.15	Pearson
Mercapto mix	135	3	2.22	912	8	0.88	0.15	Pearson
2-Hydroxyethyl acrylate	46	0	0	281	11	3.92	0.17	Pearson
Gold sodium thiosulfate	136	18	13.24	935	168	17.97	0.17	Pearson
Triclosan	136	2	1.47	911	4	0.44	0.18	Fisher
Bacitracin	136	15	11.03	924	142	15.37	0.18	Pearson
Euxyl K400	135	5	3.70	919	61	6.64	0.19	Pearson

PCMX = 4-Chloro-3,5-xyleneol (chloroxylenol).

Table 3 shows the most common positive patch-test reactions in each group. These are similar except that Compositae mix appears in the top 10 only for the AD patients.

Discussion

For atopic patients tested after systemic antibiotics were used to calm active disease and when patch tests were interpreted at day 7 to minimize irritant responses, there was no difference between their overall number of positive patch-test results and that of nonatopic patients.

Numerous comparisons were made for individual allergens, such that a single significant association must be interpreted with caution. However, it is notable that PCMX, which can cross-react with chlorocresol (PCMC)

used to preserve topical medicaments, was the only allergen that differed significantly, and it was more common in the AD group. Many of the allergens that were overrepresented in the atopic patients are components of topical medicaments (eg, stearyl alcohol, propylene glycol, and tixocortol pivalate) although these differences were not significant. Patients with AD may have been more likely to seek medical advice for rash and therefore to use these medicaments, whereas nonatopic patients are more likely to use over-the-counter antibiotic ointments, which are heavily advertised in the United States. Nonatopic patients were more likely to have positive patch-test reactions to neomycin and bacitracin although this trend was not significant.

Patients with AD have a lower irritancy threshold,¹⁴ making it difficult to interpret weak reactions at early readings.¹⁵ A delayed reading at day 7 is especially useful with AD patients, in whom irritant responses to patch tests are likely. This appears to reduce the problem of irritant results in our data, whereas previous interventions (such as diluting the patch-test concentration of marginal irritants) were unsuccessful.¹⁶ The percentages of positive patch-test reactions to the common irritants Euxyl K400 (methyl dibromoglutaronitrile with phenoxyethanol), potassium dichromate, and dithiomorpholine were all higher in non-AD patients than in AD patients in this study (data not shown).

Table 3. Most Common Allergens Causing Positive Patch-Test Reactions in Atopic and Nonatopic Dermatitis Subjects

<i>AD Patients</i>	<i>Non-AD Patients</i>
Nickel sulfate	Nickel sulfate
Thimerosal	Bacitracin
Cobalt (II) chloride hexahydrate	Cobalt (II) chloride hexahydrate
Quaternium-15	Balsam of Peru
Formaldehyde	Quaternium-15

AD = atopic dermatitis.

These data (1) suggest that AD patients should be patch-tested and (2) further the recent recommendation that the subpopulation of AD patients in the high-risk occupation of hairdressing be patch-tested.¹⁷

Limitations

All subjects were part of the same investigator's practice. A high degree of suspicion was required before AD patients were patch-tested. This may have inflated the yield of patch-test results.

There was no control group of patients with active disease not treated with antibiotics and systemic azoles. Therefore, comparison is retrospective to other studies in which methods also differed (such as the definition of AD, the timing of readings, etc).

Conclusions

First, patients with atopic dermatitis (AD) have positive patch-test reactions to standard nonprotein allergens at a rate similar to that of non-AD patients. Relevance is best determined by observing the resolution of dermatitis with the avoidance of identified allergens, but AD patients may flare because of numerous triggering factors that are not identified by conventional patch testing, to the extent that it is more difficult to determine the relevance of patch-test results.

Second, AD patients should be patch-tested with the components of topical medicaments (eg, corticosteroids and propylene glycol) and Compositae mix (relevant, for example, to feverfew in anti-itch medicaments).

Third, because occlusion itself can cause inflammation in AD patients, 48-hour readings immediately after patch-test removal are of minimal value. Day-7 readings are more likely to indicate a true allergic response than an irritant response, especially in AD patients.

Finally, to decrease inflammation due to commensal organisms under the patch tests, commensal staphylococcal colonization (and *Malassezia* yeast in adults) should be reduced before testing.

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